Clinical Implications of Basic Research

Apoptosis and Heart Failure

PROGRAMMED cell death (apoptosis) was unknown to William Osler and Paul Dudley White, but physicians today must grapple with the uneasy knowledge that all of our cells actively maintain the machinery of self-destruction and must continuously hold it in check to avoid that fate.

Apoptosis was first observed as a driving force that shapes the structure of tissues during embryonic development. A familiar example is the separation of the digits of our hands and feet from the blunt ends of the fetal limbs. Today, we also recognize apoptosis as a mechanism whereby damaged cells are removed from the body during adult life, a process in which individual cells sacrifice themselves to enhance the overall health of the organism. The adaptive value of the ability of programmed cell death to eliminate malignant cells is clear, and both the present and the future of cancer therapeutics are grounded to a considerable extent in ways of stimulating apoptosis selectively in tumor cells. But what about cardiovascular medicine? What, if anything, does apoptosis have to do with heart diseases, particularly ischemic heart disease and congestive heart failure, the most frequent causes of death in industrialized societies?

From a teleologic perspective, it seems illogical that adult cardiomyocytes should maintain the molecular machinery of apoptosis. Cardiomyocytes formed during fetal or early perinatal life must last a lifetime, since most authorities agree that once destroyed, adult cardiomyocytes are not replaced. The ability of the myocardium to sustain contractile function with fewer cardiomyocytes is limited, and clinical heart failure ensues once the loss of contractile units passes a critical threshold. Nevertheless, cardiomyocytes do appear to undergo apoptosis in the adult heart and are driven to do so by a variety of stimuli, including myocardial ischemia or pressure overload leading to congestive heart failure. This conclusion is supported by a burgeoning literature: more than 350 papers concerning apoptosis in the heart have been published since 1997. Conventional assays to detect cells undergoing apoptosis may yield spurious results in uncritical or inexperienced hands, and the ability to make an accurate assessment of cardiac apoptosis is complicated by the rapidity of the process and the difficulty in distinguishing myocytes from other types of cells that reside within the ventricular wall. Nevertheless, the evidence now solidly supports the conclusion that apoptosis of cardiac myocytes is a feature of both ischemic and nonischemic cardiomyopathies. The critical questions now become: To what extent does the programmed cell death of cardiomyocytes contribute to functional deterioration? Can we develop effective new therapies based on the blockade of apoptotic pathways in the heart?

A recent paper by Hirota et al.[1] takes an important step forward in this area of research. Using an advanced gene-targeting strategy — conditional, tissue-specific gene knockout — they created mice that, as adults, lack the gp130 cytokine receptor in cardiomyocytes. The gp130 protein forms heterodimeric complexes with other cytokine-receptor proteins to bind ligands of the interleukin-6 family of cytokines and to transduce signals to the interior of the cell that reprogram the expression of genes. The consequences of gp130-dependent signaling in isolated cardiomyocytes grown in cell culture include hypertrophic growth of cells and enhanced survival in the face of conditions that otherwise induce apoptosis (e.g., the removal of survival factors). Conventional gene-knockout strategies to eliminate this receptor or its cognate ligands from all cells of the body resulted in death during the embryonic stage with abnormalities in multiple organ systems, so that no conclusions about the function of this receptor in the adult heart could be drawn.

In the study by Hirota et al., the knockout mice developed normally and had grossly normal cardiac structure and function as adults. This finding indicates that gp130 is not necessary for cardiac growth under normal conditions. However, pressure overload created surgically by constriction of the transverse aorta, a model designed to mimic the effects of systemic hypertension or aortic-valve disease in humans, had dramatic consequences for these mice. During the first seven days after aortic constriction, control animals with normal levels of gp130 survived and exhibited compensatory left ventricular hypertrophy without heart failure, whereas the animals with reduced expression of gp130 in cardiac myocytes had a markedly increased rate of apoptosis in cardiomyocytes, and more than 90 percent died of dilated cardiomyopathy.

These results demonstrate that gp130-dependent signaling events, which include activation of the STAT3 transcription factor and induction of antiapoptotic proteins such as Bcl-X_L and which function to restrain apoptosis in cardiomyocytes undergoing hypertrophic growth, are evoked by pressure overload in the heart (Fig. 1). Abrogation of the antiapoptotic effect of gp130-dependent signaling leads to massive cell death in the ventricular wall and dilated cardiomyopathy. Hirota et al. conclude, with justification, that strategies to enhance signaling through gp130, perhaps by the administration of cytokines

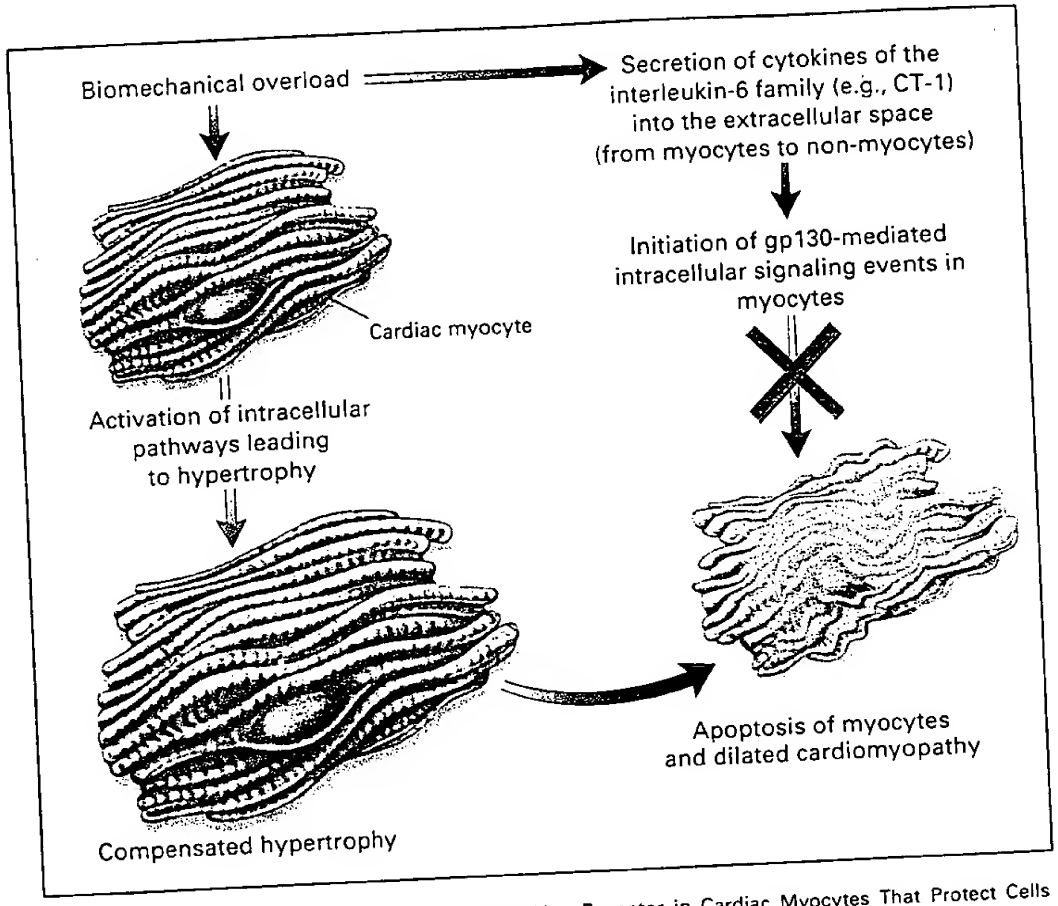

Figure 1. Signaling Events Mediated by the gp130 Cytokine Receptor in Cardiac Myocytes That Protect Cells from Apoptosis and Prevent Cardiomyopathy during Pressure-Overload Hypertrophy.

CT-1 denotes cardiotrophin-1.

of the interleukin-6 family, merit attention as potential therapeutic measures to prevent the transition from compensated cardiac hypertrophy to congestive heart failure, a major clinical goal.

The fact that endogenous levels of gp130 are required to prevent ventricular failure in the early stages of compensatory hypertrophy, however, does not necessarily imply that augmentation of gp130-dependent signaling in animals or humans with intact gp130 genes will prevent ventricular decompensation during periods of stress or modify the course of cardiomyopathy. This possibility must be assessed by additional studies in animals. Furthermore, the pleiotropic effects of interleukin-6 cytokines on other tissues, including the possibility of enhanced growth of occult tumors, may preclude the safe systemic administration of these agents or require measures to deliver them to the myocardium. Such risks must be considered carefully before studies are conducted in humans. These issues of concern, however, should not dampen the enthusiasm to translate advances in understanding of apoptotic mechanisms into novel therapeutic agents against cardiovascular disease.

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REFERENCES

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